Substitute Specification

MRD
8/6/03
ok to enter
MRM
4/19/04

Pituitary Adenylate Cyclase Activating Peptide (PACAP) Receptor 3 (R3) Agonists and Their Pharmacological Methods of Use

Field of the Invention

[001] This invention relates to newly identified polypeptides and the use of such polypeptides for therapeutic purposes. More particularly, the polypeptides of the present invention are useful in stimulating the release of insulin from pancreatic beta cells in a glucose-dependent manner, thereby providing a treatment option for those individuals afflicted with a metabolic disorder such as diabetes or impaired glucose tolerance, a prediabetic state.

Background of the Related Art

[002] Diabetes is characterized by impaired glucose metabolism manifesting itself among other things by an elevated blood glucose level in the diabetic patient. Underlying defects lead to a classification of diabetes into two major groups: type I diabetes, or insulin dependent diabetes mellitus (IDDM), which arises when patients lack beta-cells producing insulin in their pancreatic glands, and type 2 diabetes, or non-insulin dependent diabetes mellitus (NIDDM), which occurs in patients with an impaired beta-cell function and alterations in insulin action.

[003] Type I diabetic patients are currently treated with insulin, while the majority of type 2 diabetic patients are treated with agents that stimulate beta-cell function or with agents that enhance the tissue sensitivity of the patients towards insulin. Over time almost one-half of type 2 diabetic subjects lose their response to these agents and then must be placed on insulin therapy. The drugs presently used to treat type 2 Diabetes include:

[004] Alpha-glucosidase inhibitors (PRECOSE®, VOGLIBOSE™, and MIGLITOL®). Alpha-glucosidase inhibitors reduce the excursion of postprandial glucose by delaying the absorption of glucose from the gut. These drugs are safe and provide treatment for mild to moderately affected diabetic subjects. However, gastrointestinal side effects have been reported in the literature.

[005] Insulin sensitizers. Insulin sensitizers are drugs that enhance the body's response to insulin. Thiozolidinediones such as REZULIN™ (troglitazone) activate the PPAR gamma receptor and modulate the activity of a set of genes that have not been well described. Although effective, these drugs have been associated with liver toxicity. Because of hepatotoxicity, REZULIN has been withdrawn from the market.

[006] Insulin secretagogues (sulfonylureas and other agents that act by the ATP-dependent K+ channel). SFUs are standard therapy for type 2 diabetics that have mild to moderate fasting glycemia. The SFUs have limitations that include a potential for inducing hypoglycemia, weight gain, and high primary and secondary failure rates. 10 to 20% of initially treated patients fail to show a significant treatment effect (primary failure). Secondary failure is demonstrated by an additional 20-30% loss of treatment effect after six months on an SFU. Insulin treatment is required in 50% of the SFU responders after 5-7 years of therapy (Scheen, A.J., et al., Diabetes Res. Clin. Pract. 6:533-543 (1989)).